Journal of the Neurological Sciences xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Sarcoid neuropathy: Correlation of nerve ultrasound, electrophysiological and clinical findings

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ARTICLE INFO

Article history:
Received 16 August 2014
Received in revised form 15 September 2014
Accepted 19 September 2014
Available online xxxx

Keywords:
Sarcoid neuropathy
Nerve ultrasound
Cross sectional area
Electrophysiology
Functional disability
Echogenity

ABSTRACT

Introduction: We present the nerve ultrasound findings in sarcoid neuropathy and examine their correlation with electrophysiology and functional disability.
Materials and methods: 40 healthy controls and 13 patients with sarcoid neuropathy underwent clinical, sonographic and electrophysiological evaluation, a mean of 2.1 years (SD ± 0.7) after disease onset.
Results: Nerve ultrasound revealed significantly higher cross sectional area (CSA) values of the ulnar (elbow, $p < 0.001$), fibular (fibular head, $p < 0.001$), sural (between the lateral and the medial head of the gastrocnemius muscle, $p < 0.001$) and tibial nerves (ankle and popliteal fossa, $p < 0.001$), when compared to controls. The electroneurography documented significantly lower values of the 1) compound muscle action potentials (cMAPs) in the median, fibular and tibial nerves ($p < 0.001$), and 2) sensory nerve action potential (sNAP) in the median, ulnar and sural nerves ($p < 0.001$). A significant correlation between sonographic and electrophysiological findings in the group with sarcoid neuropathy was found only between cMAP and CSA of the ulnar nerve at the elbow ($r = 0.894$, $p < 0.001$). Neither nerve sonography nor electrophysiology correlated with functional disability.
Discussion: Sarcoid neuropathy seems to show predominantly CSA enlargement in peripheral nerves of the lower extremities, without any significant correlation to electrophysiological findings. The electroneurography documented signs of sensorimotor axonal loss in various peripheral nerves. Neither nerve sonography nor electrophysiology correlated with functional disability.

1. Introduction

Sarcoidosis is a polysystemic, granulomatous disorder mainly showing a pulmonary localization, while the skin, eyes, liver and lymph nodes may be also affected. 5% of patients with systemic sarcoidosis show neurological complications. In 20% of patients with neurosarcoidosis peripheral neuropathy is diagnosed, which is usually asymptomatic [3]. The most common types of sarcoid polyneuropathy are the sensorimotor and pure motor polyneuropathies and to a lesser degree the small fiber neuropathy, the acute inflammatory demyelinating polyradiculoneuritis and the lumbosacral plexopathy [15,24,31]. The definite diagnosis of sarcoid neuropathy is based on the histological demonstration of sarcoid granulomas in nerve biopsy specimens.

Utrasound detection of asymmetric, inhomogenous increase in nerve cross sectional area (CSA) of peripheral nerves has been already reported in different immune-mediated neuropathies [6–8,11,19]. Various studies reported the absence of significant correlation between sonographic, electrophysiological (mainly compound muscle action potential) and clinical findings in inflammatory neuropathies [6–8,10], showing that each diagnostic method highlights different aspects of peripheral nerve impairment.

We aimed to investigate the correlation between nerve sonography, nerve conduction studies, and functional disability in sarcoid neuropathy.

2. Material and methods

2.1. Subjects and patients

The ethics committee of the Ruhr University in Bochum, Germany approved our study protocol and all patients with sarcoid neuropathy and healthy subjects signed informed consent. Prior to the study enrolment, all healthy subjects interested in participating in this study underwent nerve conduction studies (median, ulnar, sural, tibial and fibular nerves) on both sides. Healthy subjects having symptoms, clinical or electrophysiological signs referable to peripheral nerve disease were excluded from the study. Healthy subjects or patients having a history of diabetes or alcoholism were also excluded from the study.

Overall, 40 healthy controls, aged over 18 years, were recruited in the study. In addition, 13 patients with sarcoid lesions in peripheral

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http://dx.doi.org/10.1016/j.jns.2014.09.033
0022-510X/

nerve biopsy samples were enrolled in the study. At the time point of evaluation, all patients received as a therapy, either azathioprine (2 mg/kg body weight) or infliximab (5 mg/kg body weight). Patients, that received oral or intravenous corticosteroids during the last 3 months prior evaluation, were excluded from the study.

2.2. Ultrasound examination

Ultrasonography was performed from a board certified neurologist (A.K.). All ultrasound studies have been performed with the use of an Aplio® XG ultrasound system (Toshiba Medicals, Tochigi, Japan). For the superficial nerves of the body (median, ulnar, radial, brachial plexus, tibial at the ankle, and sural) a 18-MHz linear array transducer was used, and for the deeper nerves (tibial and fibular in the popliteal fossa) a 12-MHz linear array transducer was used. The transducer was always kept perpendicular to the nerves. No additional force was applied other than the weight of the transducer and the extremities were kept in the neutral position to avoid causing any artificial nerve deformity. Cross sectional area measurements were performed at the inner border of the thin hyperechoic epineural rim by the continuous tracing technique and the average values were calculated after serially measuring three times.

All peripheral nerves and brachial plexus were measured bilaterally in all healthy subjects and patients with sarcoid neuropathy at the following sites: the median nerve at the entrance to the carpal tunnel (retinaculum flexorum), forearm (15 cm proximal to the retinaculum flexorum), upper arm (middle of the distance between the medial epicondyle and axillary fossa), ulnar nerve at Guyon's canal, forearm (15 cm proximal to Guyon's canal), elbow (between the medial epicondyle and olecranon), upper arm (middle of the distance between the medial epicondyle and axillary fossa), radial nerve in the spiral groove, tibial nerve in the popliteal fossa and at the ankle, fibular nerve at the fibular head and in the popliteal fossa and sural nerve (between the lateral and the medial head of the gastrocnemius muscle). The brachial plexus was also assessed in the supraclavicular (next to the subclavian artery) and interscalene spaces.

After obtaining the CSA values in each predefined site of clinical interest, we performed an ultrasound scan of the complete course of the median and ulnar nerves from proximal (axillary fossa) to distal (carpal tunnel for the median nerve and Guyon's canal for the ulnar nerve), in order to measure the maximal and minimal cross sectional areas of each nerve. Maximal CSA was defined as: the site in the course of the nerve with the maximal area at the inner border of the thin hyperechoic epineural. Similarly, minimum CSA was defined as: the site in the course of the nerve with the minimal area at the inner border of the thin hyperechoic epineural rim.

For the quantification of ultrasound findings we used the recently proposed measures in the literature [10–13,20]. Therefore, we calculated for each peripheral nerve and brachial plexus the intranerve-, internerve-, and intraplexus CSA variabilities and "side to side difference ratio of the intranerve CSA variability". Due to anatomic limitations in the imaging of the nerves of the lower extremities (short visualizable length of the fibular and tibial nerves) we used for the calculation of the above measures, the CSA values acquired from the predefined sites of interest. All patients underwent sural nerve biopsy, so no documentation of the complete anatomic course of the sural nerve was done. Therefore, only the CSA of the sural nerve at one site is included in this study. Due to the short visualizable course of the brachial plexus as a unique entity, we used for the calculation of this measure the CSA values acquired from the supraclavicular and interscalene spaces.

2.3. Nerve conduction studies

All the electrophysiological studies were performed from a board certified neurologist (M.-S. Y.) with the use of a Medtronic 4 canal electromyography device (Medtronic, Meerbusch, Germany). All testing

Table 1
Overview of the sonographic results in the neurosarcoidosis and control groups.

		Neurosarcoidosis (n = 13)		Controls (n = 40)		Upper cut-off	p
		Mean	SD	Mean	SD		
Age		59.8	19.	53.2	12.1		0.15
Nerve	Site						
Median	Carpal tunnel	9.78	4.80	8.37	2.10	12.57	0.143
	Forearm	6.85	1.79	6.62	1.60	9.82	0.661
	Upper arm	8.92	2.80	8.28	2.55	13.38	0.442
	Intranerve CSA variability	1.56	0.33	1.10	0.15	1.40	**<0.001**
	SSDIVA	1.23	0.44	1.22	0.14	1.50	0.890
Ulnar	Guyon's canal	5.42	1.69	5.12	1.31	7.74	0.500
	Forearm	5.57	1.86	5.30	1.22	7.80	0.552
	Elbow	8.42	2.59	5.41	1.40	8.21	**<0.001**
	Upper arm	7.28	2.30	6.60	1.61	9.80	0.282
	Intranerve CSA variability	1.80	0.65	1.52	0.48	2.48	0.097
	SSDIVA	1.33	0.44	1.23	0.21	1.65	0.271
Radial	Spiral groove	4.28	1.89	3.21	1.48	6.17	0.039
Brachial plexus	Supraclavicular space	56.92	19.91	46.80	13.27	73.34	0.047
	Interscalene space	33.21	12.22	30.25	10.10	50.45	0.387
	Intraplexus CSA variability	2.00	0.82	1.59	0.37	2.33	0.015
	SSDIVA	1.40	0.32	1.20	0.15	1.5	0.003
Fibular	Fibular head	9.71	3.64	6.86	2.05	10.96	**<0.001**
	Popliteal fossa	9.07	1.77	8.49	2.14	12.77	0.381
	Intranerve CSA variability	1.52	0.30	1.31	0.32	1.95	0.042
	SSDIVA	1.36	0.25	1.17	0.25	1.67	0.021
Tibial	Popliteal fossa	13.50	4.75	8.40	2.52	13.44	**<0.001**
	Ankle	11.42	3.83	6.31	1.42	9.15	**<0.001**
	Intranerve CSA variability	1.50	0.43	1.39	0.28	1.95	0.289
	SSDIVA	1.32	0.21	1.29	0.44	2.61	0.814
Sural	Between the lateral and the medial head of the gastrocnemius muscle	2.42	0.75	1.83	0.41	2.65	**<0.001**
	Internerve CSA variability	2.24	0.49	1.71	0.57	2.85	**<0.001**

All values are calculated in mm^2. CSA = cross sectional area, SD = standard deviation, SSDIVA = side to side difference ratio of the intranerve cross sectional area variability. p-Values - 0.001 were considered as statistically significant and are highlighted with bold. Upper cut-off reference values of the CSA were defined as mean value + 2 standard deviation (SD).

Please cite this article as: Kerasnoudis A, et al, Sarcoid neuropathy: Correlation of nerve ultrasound, electrophysiological and clinical findings, J Neurol Sci (2014), http://dx.doi.org/10.1016/j.jns.2014.09.033